> fragments thereof) can prevent a previously primed T cell (i.e., one sensitized to a particular autoantigen) from activating and triggering an immune response.

There are many examples throughout the specification which refer to the use of agonists as autoantigens such as page 9, line 5 of the published PCT application. Applicant respectfully requests withdrawal of the rejection of claims 1 - 7 and 21 - 28 pursuant to 35 USC 112(1).

Sequence Listing

The PTO requested a Sequence Listing in compliance with 37 CFR 1.821 - 1.825. Pursuant to 37 CFR 1.821(e) and MPEP 2422.05, applicant refers to U.S. Patent Application Serial No. 09/111,123 which has sequence listings of peptides identical to those which are listed in the present application. A computer readable form was filed in that application. A letter is attached requesting the use of the previously filed information. A paper copy is provided of the Sequence Listing which is identical to the sequence listings in the computer readable form. No new matter is added.

Rejection of the Claims under 35 USC 103(a)

Claims 1 - 7 and 21 - 28 stand rejected under 35 USC 103(a) as being unpatentable over Bona et al. in view of Liu and Karpus. Applicant respectfully disagrees with the rejection. There is no teaching in Bona of the claimed invention of the present application. None of the compositions disclosed in Bona, Liu or Karpus are capable of reducing a T cell mediated inflammatory response as do the claimed compositions of the present application. In fact, Bona teaches the use of peptides derived from viral proteins into immunoglobulins to *generate* an immune response. One of ordinary skill in the art, in reviewing the Bona, Liu and Karpus references, would not be led to claimed compositions of the present application.

The Bona reference speculates in a throw away sentence at the end of the document that:

> The method can be extended to express other biologically important epitopes such as tumor antigens, oncogenes or self antigens which can be used in the antitumor therapy of the therapy of autoimmune disease. In the later cases, it is possible that the Ig bearing epitopes of self antigens will be more efficient for peptide competition therapy envisioned as a novel immunotherapeutic approach of autoimmune diseases (Adorini *et al.*, 1990). The beneficial effect of Ig containing

self epitope versus synthetic peptide is related to their longer half life and efficacy in binding generated peptides to newly synthesized MHC antigens.

However, the phrase "self antigens", as used in Bona, does not refer to molecules which interact with T cells responsible for the autoimmune disease and does not teach or suggest the "T cell peptide receptor agonists" of the claimed invention. The peptide competition therapy which Bona references has nothing to do with the claimed compositions or the mechanism by which the claimed compositions down-regulate autoreactive T cells. The Adorini article (a copy of which is attached) teaches the use of non-pathogenic self-peptides (peptides which are unrelated to the peptides against which the T cells respond) to out compete the peptides against which the autoimmune reaction is mounted. What Adorini teaches and what Bona suggests by referring to Adorini, is that because the MHC Class II molecules would be presenting non-pathogenic peptides, the pathogenic peptides would be unable to bind to the MHC Class II molecules ("peptide competition") thereby possibly lessening the autoimmune reaction. Thus, Bona merely speculates that self antigens could be inserted into immunoglobulins and introduced into cells to out compete pathogenic peptides. However, the mechanism suggested in Bona would probably not work to lessen or stop an autoimmune response because MHC molecules and pathogenic peptides are constantly being synthesized in unlimited amounts inside the antigen presenting cells (APCs) and the introduced peptide would be out competed over time. At best, a transitory competition might occur and whether this would actually result in lessening or prevention of an autoimmune response even for a short period of time is open to question. Bona is merely speculating and provides no examples, data or results to support the hypothesis. Thus, applicant believes that the combination of Bona in view of Liu and/or Karpus is not enabling prior art for the purpose asserted by the Examiner.

The compositions of the present invention reduce an autoimmune disorder by an immunoglobulin carrying the T cell receptor agonist inside the antigen presenting cell ("APC"). Once inside the APC, the immunoglobulins are processed by endosomes resulting in the cleaving of the peptide and formation of a complex with newly synthesized MHC molecules. The resulting MHC - peptide complexes migrate to the cell surface where they engage autoreactive T cells. This engagement induces a TCR triggered signaling event, resulting in alteration of cytokine production and reduction of the T cell mediated inflammatory reaction. The claimed compositions and

mechanism by which they are used to treat an autoimmune disorder are entirely different than what is taught in Bona and Adorini and the deficiencies are not cured by the addition of Liu and/or Karpus.

Liu simply teaches the use of free peptides and examines variants of the immunodominant peptide of myelin basic protein (by single amino acid substitution) in an attempt to determine what amino acid substitutions might improve binding of the peptide to the MHC complex of the APCs. However, there is no teaching or suggestion in Liu to insert peptides into an immunoglobulin. Karpus refers to the feeding of free PLP agonists peptides to mice. There is no teaching or suggestion in Karpus to insert a peptide into an immunoglobulin.

Bona in view of Liu and/or Karpus do not teach or suggest the claimed invention. One of ordinary skill in the art in reviewing Bona in view of Liu and/or Karpus would not have been led to the compositions of the claimed invention. None of the compositions taught by Bona interact with T cells responsible for the autoimmune disease and thus Bona does not teach or suggest the use immunoglobulins coupled to a "T cell receptor peptide agonist" as required by the claims of the present application. None of the referenced prior art references taken separately or together teach or suggest insertion of a T cell agonist into an immunoglobulin backbone thereby resulting in suppression of disease by T cell receptor engagement and alteration of cytokine expression. Applicant thereby respectfully requests withdrawal of the rejection under 35 USC 103.

Applicant has filed the response with a three month extension of time. If there are any questions concerning this response, applicant's attorney can be reached at the telephone number stated below.

Dated: 12/24/02

By: _____
John Wurst
Registration No. 40,283
(858) 410-5174